

Environmental and Population Studies Concerning Exposure to Pesticides in Iran: A Comprehensive Review

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Received: July 28, 2013; Revised: December 2, 2013; Accepted: October 27, 2013

Pesticides are widely used in Iranian agriculture and this has made a major toxicological concern among health professionals. The objective of this study is to explore national data about pesticides toxicity. All relevant databases such as Google Scholar, PubMed, and Scopus in a time period of 1960 to 2012 were searched for the keywords "Pesticides, Iran, Environment, and Population studies". A total of 57 studies were found relevant and then included into study. Almost all non-experimental studies carried out in Iran were classified into two main categories of residue assessment in different samples and toxic effects on human. Depending on the dose and duration of exposure, toxic effects of pesticides have been studied in two classifications including acute toxicity or acute poisoning and chronic toxicity. High extent of pesticides have been used during the past decade in Iran while no enough proper studies were done to explore their possible toxic effects in the environment and the people.

Keywords: Pesticides; Iran; Environmental; Population

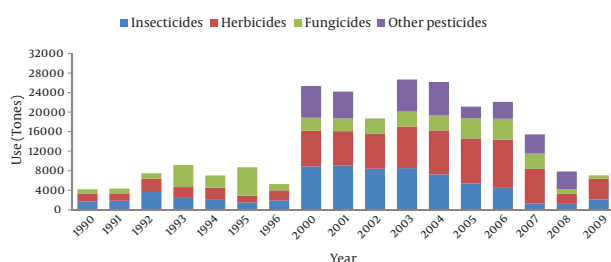
1. Context

Pesticides are considered as a main tool in modern agriculture regarding their potential to control pests and vectors of diseases but knowing their hazards for environment and human health has given rise to controversy on the excessive use of these chemicals. They constitute a large group of chemicals which upon their target are classified into different subgroups like insecticides, herbicides, fungicides, etc. Pesticides dependent agriculture and their widespread use have become an issue of concern in Iran as 18.5 million hectares are cultivated by 3.4 million farmers. Insecticides have become the most used

and others (5.5%) (www.pan-uk.org). Beginning in 2000, pesticides' use has been dramatically increased in Iran and reached to the ultimate in 2003-2004 given by annual usage of 27000 tones throughout the country (Figure 1) (www.faostat.fao.org).

In order to evaluate the burden of pesticide exposure at public level, different types of population studies have been carried out in the country. In this review, we have gathered all and discussed environmental and population studies related to pesticides exposure in Iran in order to have an overview of ways on which pesticide focused researches should take steps, find the lacks of current information in evaluating the level of pesticides burden, and take clues and approach to direct the perspectives.

Figure 1. The Rate of Pesticides' Use in Iran During 1990-2009



Data were extracted from Food and Agriculture Organization of the United Nations (www.fao.org).

pesticides in Iran (33%), followed by herbicides (30%), fungicides (20 %), acaricides (6.2%), rodenticides (3.8%), nematicides (1.5%)

2. Evidence Acquisition

In order to make a comprehensive review, Google Scholar, PubMed, and Scopus were searched between the years 1960 to 2012 for the keywords "Pesticides, Iran, Environment, and Population studies". A total of 215 articles were found in primary search but after elimination of duplicates or irrelevant papers, only 57 records remained to be reviewed (Table 1). Almost all non-experimental studies carried out in Iran were classified into two main categories of residue assessment in different samples and toxic effects in human. Depending on the dose and duration of exposure, toxic effects of pesticides have been studied in two classifications including acute toxicity or acute poisoning and chronic toxicity. The number of studies in each category is shown in Figure 2.

Implication for health policy/practice/research/medical education:

Exposure to pesticides has been shown to be associated with higher prevalence of chronic diseases which needs to be specifically evaluated in the country.

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Table 1. List of Environmental and Population Studies on Health Effect of Pesticides in Iran

Study	Model	Sample	Pesticide	Result
Sodergren et al. 1978	Residue assessment	Fish (rivers), Sediments (drainage sys)	DDT, PCBs	High level of DDT, Low level of DDT and PCBs
Esfahani et al. 2012	Residue assessment	Sediments and water from wetlands	Chlordane, lindane, endosulfan	Most frequently: chlordane, lindane, and endosulfan
Fadaei et al. 2012	Residue assessment	Surface water	Malathion, diazinon	> Allowed limits
Rezaee et al. 2012	Residue assessment	Tap and bottled mineral water	Aldicarb, parathion, thiobencarb	< WHO limits
Shayeghi et al. 2007	Residue assessment	Drinking water	Malathion, diazinon	> Allowed limit
Bayat et al. 2011	Residue assessment	Commercial pasteurized milk	DDT derivatives, PCBs	ADI of PCBs > FAO/WHO limit
Kalantzi et al. 2001	Residue assessment	Butter	DDT, DDT isomers, HCB, HCH	DDT, HCB, and HCH > global average
Jafari et al. 2008	Residue assessment	Butter	POPs	PCBs, p,p'-DDT and p,p'-DDE > global average 2001
Dahmardeh et al. 2012	Residue assessment	Hair samples of pregnant women	DDT, HCB, HCH, and seven PCBs	Significant different on locations and fish consumption
Hashemy-Jonkabony and Fatemi-nassab 1977	Residue assessment	Milk of nursing mothers	DDT, BHC, dieldrin	Dieldrin > WHO limit
Cok et al. 1999	Residue assessment	Human milk	BHC, HCB, DDT, heptachlor epoxide	BHC, HCB, heptachlor epoxide > FAO/WHO established ADI
Behrooz et al. 2009	Residue assessment	Human milk	OCs, PCBs	OC pesticides and PCB > infant daily intake established by Health Canada
Hashemy-Jonkabony and Soleimani-Amiri 1978	Residue assessment	Human adipose tissue	OCs	Moderate exposure to HCB, DDT and light exposure to dieldrin
Burgaz et al. 1995	Residue assessment	Human adipose tissue	OCs	HCB as the highest contaminant
Ghazi-Khansari and Oreizi 1995	Prospective	Poisoning patients	General	Most death due to pesticides (58 %)
Abdollahi et al. 1997	Retrospective	Poisoning patients	General	Most death due to pesticides (19.2 %)
Moghadamnia and Abdollahi 2002	Epidemiologic	Poisoning patients	General	Most death due to pesticides
Islambulchilar et al. 2009	Descriptive, Retrospective	Poisoning patients	General	Most death due to pesticides
Ahmadi et al. 2010	Descriptive, Retrospective	Poisoning patients	General	Most death due to pesticides
Soltaninejad et al. 2007	Retrospective	Un-survived poisoning	General	Most death due to pesticides; ALP > OP
Shadnia et al. 2007	Descriptive, Retrospective	Poisoning patients	General	OPs the main pesticides in poisoning
Ghazinoor et al. 2009	Retrospective, Descriptive	Poisoning patients	General	Pesticides among the most common causes for parasuicide
Ranjbar et al. 2005	Clinical, Descriptive	Poisoning patients	OPs	↓AChE activity, ↑Oxidative stress
Soltaninejad et al. 2007	Clinical, Descriptive	Poisoning patients	OPs	Blood β-glucuronidase as a biomarker at acute poisoning
Shadnia et al. 2009	Clinical, Descriptive	Poisoning patients	OPs	Prolonged QTC interval ~ prognosis of poisoning
Jalali et al. 2010	Clinical, Descriptive	Poisoning patients	OPs	Distal sensory deficit on EMG
Noshad et al. 2007	Clinical, Retrospective	Poisoning patients	OPs	Respiratory failure ~ mortality
Sabzghabaei et al.	Clinical, Descriptive	Poisoning patients	Paraquat	PQ dose, vomiting and age as important variables in the mortality
Soltaninejad et al. 2011	Clinical, Descriptive, Case report	Poisoning patient	ALP	Met-Hb and Hemolysis as complications

Shadnia et al. 2010	Clinical, Descriptive, Case report	Poisoning patients	ALP	Met-Hb and Hemolysis as complications
Mostafazadeh et al. 2011	Clinical, Descriptive, Prospective	Poisoning patients	ALP	Met-Hb ~ rate of mortality
Sanaei-Zadeh 2012	Clinical, Descriptive	Poisoning patients	ALP	Blood Met-Hb ~ patient outcome
Mehrpour et al. 2008	Clinical, Descriptive	Poisoning patients	ALP	Hyperglycemia ~ mortality
Shadnia et al. 2009	Clinical, Descriptive	Poisoning patients	ALP	Blood pH ~ patients outcome
Soltaninejad et al. 2012	Clinical, Descriptive	Poisoning patients	ALP	Dysrhythmia, elevated ST, prolonged QT, ↑cardiac troponin-T
Shadnia et al. 2008	Clinical, Descriptive, Case report	Poisoning patients	ALP	Rapid inhalational absorption, hyperglycemia, surviving
Shadnia et al. 2011	Clinical, Descriptive, Prospective	Poisoning patients	ALP	Simplified Acute Physiology Score II to predict outcome
Saleki et al. 2007	Clinical, Descriptive	Un-survived poisoning patients	ALP	Cytoplasmic vacuolization of hepatocytes and sinusoidal congestion
Shadnia et al. 2005	Clinical, Interventional, Case report	Poisoning patients	ALP	Benefit of coconut oil in the treatment
Abdollahi et al. 1995	Clinical Interventional	Poisoning patients	OPs	Use of atropine alone in the treatment of poisoning
Balali-Mood and Shariat 1998	Clinical, Interventional	Poisoning patients	OPs	Benefit of PAM + atropine
Pajoumand et al. 2004	Clinical, Interventional	Poisoning patients	OPs	Benefit of magnesium sulfate
Balali-Mood et al. 2005	Clinical, Interventional	Poisoning patients	OPs	Benefit of sodium bicarbonate
Shadnia et al. 2011	Clinical, Interventional	Poisoning patients	OPs	Benefit of NAC
Afzali and Gholyaf 2008	Clinical, Interventional	Poisoning patients	Paraquat	Benefit of cyclophosphamide, methylprednisolone
Tehrani et al. 2012	Clinical, Interventional	Poisoning patients	ALP	Benefit of NAC
Abdollahi et al. 1995	Chronic Biomarkers	Manufacturing workers	OPs	Correlation between plasma AChE and symptoms of poisoning
Abdollahi et al. 1996	Cross-sectional	Manufacturing workers	OPs	Correlation between AChE activity in plasma and saliva
Joshaghani et al. 2007	Chronic Biomarker	Manufacturing workers	Pesticides	↓ ChE activity in serum and RBC
Shadnia et al. 2005	Chronic Biomarker	Manufacturing workers	OPs	↑ Oxidative stress, DNA damage
Ranjbar et al. 2002	Chronic Biomarker	Manufacturing workers	OPs	↓ AChE activity, ↑ oxidative stress
Shayeghi et al. 2009	Chronic Biomarker	Spray workers	OPs, Carbamates	↓ AChE
Bayrami et al. 2012	Chronic Biomarker Cross-sectional	Horticulture farmers	OPs	↑ Oxidative stress
Vandekar et al. 1968	Chronic Biomarker	Spray workers	O-isopropoxy phenyl methyl carbamate	↓ AChE
Ranjbar et al. 2002	Chronic Biomarker	Manufacturing workers	Paraquat	↑ Oxidative stress
Zakerinia et al. 2012	Chronic Disease Retrospective, case control	Exposed people	Pesticides	↑ Risk of non-Hodgkin lymphoma and multiple myeloma
Malekiran et al. 2013	Chronic Diseases, Cross-sectional	Farmers	OPs	↑ Risk of diabetes and neuropsychological disorders

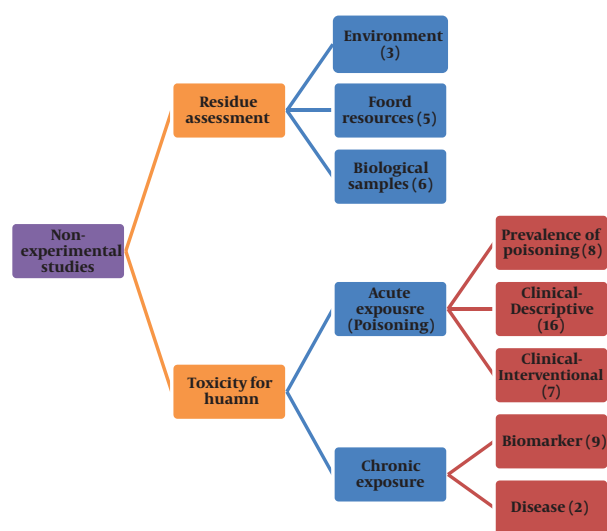


Figure 2. The Main Categories of Pesticides-associated Studies Carried Out in Iran

3. Results

3.1. Presence of Pesticides Residue

In a study carried out in Mashhad, concentration of aldicarb, parathion, and thiobencarb in the water was measured by gas chromatography and the results were lower than WHO limits (1). Contrary to these results, the amounts of malathion and diazinon were more than allowed limits in the water in Mazandaran (2). There is a same report on the residues of malathion and diazinon in the water collected from places close to agricultural lands in Tehran 1-2 months after spraying (3). The first study on OC pesticides level in water and soil in Iran was performed in 1974. The results implicated high levels of DDT in fish taken from two rivers in southern Iran and low levels of DDT and polychlorinated biphenyls (PCBs) in the samples of sediment from the drainage systems in Tehran (4). Recently, Esfahani et al. (2012) conducted a study from 2009 to 2010 and showed that the most frequent pesticides in sediment and water samples taken from Amir-kalaye wetland were chlordane and then lindane in the summer and lindane and endosulfan in the winter (5).

In a study on commercial pasteurized milk, the levels of DDT derivatives and PCBs were reported to be lesser and higher than the ADI established by FAO/WHO, respectively (6). Furthermore, the concentrations of DDT and its isomers, HCB, and HCH in Iranian butter samples, especially in the central parts of the country were shown to be higher than those found in a global study (7). The highest concentrations of PCB have been found in the samples from Mazandaran province in the North and from industrialized cities such as Tehran, Isfahan and Arak (8).

Dahmarde and colleagues measured OC level in hair samples of pregnant women in 2007 and 2008 in Ahvaz and Noushahr cities. Concentration of PCBs was significantly higher in Ahvaz than those in Noushahr and their countryside. Concentration of DDT metabolites was reported to be high in the hair samples taken from countryside of Noushahr (9). Between the years 1974-1976 throughout Tehran area, 131 human milk samples were collected and analyzed for DDT, BHC, and dieldrin by gas-liquid chromatography and the results indicated that the mean concentration of dieldrin exceeded the WHO limit (10). Later, a same study was conducted on 40 human milk samples and daily intake of BHC, HCB, heptachlor epoxide but not DDT for breast-fed children was reported to be higher than ADI established for adults by FAO/WHO Expert Groups (11). In addition, a survey carried out in Nour and Noushahr cities in 2006 indicated that the daily intake of OC pesticides and PCBs for infants via breast milk was above the guideline proposed by Health Canada (12). Only a few reports regarding the levels of OC contaminants in adipose tissue are available for Iran but in a study, HCB was reported as the highest contaminant in human adipose tissues from 1991-1992. In this regard, data collected from a study during 1974-1976 are representative of relatively moderate exposure to DDT and BHC and relatively light exposure to dieldrin (13,14).

3.2. Prevalence of Pesticide Poisoning

In the north of Iran and Tabriz, OP and carbamate insecticides have been reported as the third major agents detected for poisoning and death (15-17). In Tehran, between 1994-1995 and 2003-2004, the result of a couple of studies showed that the most fatal poisoning cases were related to pesticides most commonly aluminum phosphide (ALP) and then OP (18-23).

3.3. Biomarkers of Disruption Following Exposure to Pesticides

3.3.1. Organophosphoruses (OPs) and Carbamates

Abdollahi et al. evaluated the level of AChE in samples of healthy and occupationally OPs exposed people in two separate studies and directed well correlation between plasma and erythrocyte ChE (24, 25). A study conducted by Joshaghani and colleagues indicated that the level of ChE activity in the samples of 63 pesticide workers was significantly lower than those of normal group (26). The same results were previously reported by Ranjbar and colleagues in two separate studies on 22 poisoned patients and 45 formulating workers, respectively (27, 28). Measurement of ChE inhibition can be helpful in the management of carbamate and OP poisonings, while in chronic exposures, before/after comparison of this value can produce more acceptable data (29, 30).

Because of variable ChE activity among different persons and lack of pre-exposure data in poisoned patients, the researchers attempt to find other diagnostic factors for management of poisoning. Electrocardiography of OPs poisoned patients was studied and a significant relation between reduction of QT interval and ChE inhibition and mortality rate was found (31). Recently, evaluation of electromyography (EMG) of OPs pesticides poisoning cases with polyneuropathy sings has been conducted in Mashhad by Jalali and colleagues. That study showed a significant dysfunction in sensory rather than motor neurons affecting lower extremities, particularly tibial and peroneal nerves, more than upper extremities (32). In another study conducted on four of 98 chemical warfare victims, with severe mustard gas exposure and mean age of 49.8 years, EMG findings revealed positive sharp waves as well as fibrillations. The motor unit action potential defects in these cases indicated presence of axonal polyneuropathy (33).

Genotoxic potential of OPs pesticides was indicated in a study carried out on 21 pesticide formulators. This result was accompanied with a significant elevation in the activity of anterythrocyte antioxidant enzymes such as catalase, superoxide dismutase (SOD) and glutathione peroxidase (34). Increased level of SOD and lipid peroxidation (LPO) was also reported in the samples of 40 horticulture farmers (35) in 22 poisoned patients (28), and in 45 pesticide formulators (27). Blood β -glucuronidase has been also investigated and suggested as a suitable biomarker for not only chronic but also acute OP poisoning in human (36). In treatment of poisoning, few clinical studies indicated that infusion of high doses of NaHCO_3 , intravenous magnesium sulfate, and high doses of pralidoxime appears to be beneficial in treatment of patients with OP poisoning (21, 37-39). Although, some reported that atropine alone can be beneficial enough in the management of OP poisoning (40). Furthermore, it has been reported that NAC as a typical antioxidant have beneficial effects on outcome of OP challenged patients when it is used as an adjunct therapy to the standard protocol (41).

3.3.2. Paraquat (PQ)

Mortality rate of PQ poisoning in Iranian hospital was reported 50% (42) of which 81.8% (43) showed a positive correlation with age of patients and also occurrence of vomiting after ingestion (42). Intravenous infusions of cyclophosphamide (15 mg/kg) daily for two days and methylprednisolone 1 g daily for three days decreased the mortality rate of paraquat poisoning by 33.3% (43). In a chronic exposure study on paraquat-formulators, increased LPO and decreased antioxidant power were reported (44).

3.3.3. Aluminum Phosphide (ALP)

There are some reports on the occurrence of mild hyperglycemia following ingestion of ALP (45, 46) and also higher level of blood glucose in non-survivors hypothe-

sizing that there is a correlation between hyperglycemia and the rate of ALP-induced mortality (47-49). Induction of oxidative stress along with protective effect of NAC against LPO markers in the plasma of ALP-poisoned patients have been recently reported (50). Further, ALP has been shown to cause cytoplasmic vacuolization of hepatocytes and sinusoidal congestion in 38 fatal poisoning cases (51). In a retrospective study on 471 ALP-poisoned patients, 93% of cases were self-poisoning. Cardiovascular disorders were the most common signs of poisoning in which correction of blood pH and HCO_3 concentration seemed helpful in reduction of mortality (52). Soltaninejad et al. (2012) recorded dysrhythmia, elevated ST segment, and prolonged QT interval in ECG monitoring of 20 patients, as well as a positive serum cardiac troponin-T in 30-40% of patients (53). These researchers developed a simplified acute physiological score according to the demographic data as a prognostic and predictor tool in ALP poisoning (54). An association was found between methemoglobinemia and mortality rate of ALP poisoning which can be treated by methylene blue and ascorbic acid. Beneficial effects of hyperbaric oxygen therapy and exchange blood transfusion have been reported in two ALP poisoned patients who were resistant to methylene blue and ascorbic acid treatments (45, 55-59).

3.4. The relationship Between Exposures to Pesticides and Diseases

A retrospective study conducted in Nemazee Hospital, Shiraz in 2007-2008 showed that pesticide-exposed cases were at a higher risk of non-Hodgkin lymphoma and multiple myeloma (60). Noshad et al. (2007) indicated 12.5% respiratory failures accompanied with 50% mortality in pesticide-poisoned patients admitted to Sina Hospital, Tabriz from 2002 to 2005 (61). A cross-sectional analysis of 187 chronically OP-exposed farmers showed an increased possibility of neuropsychological disorders and metabolic diseases mainly diabetes (62). Another cross-sectional analysis of 40 farmers dealing with pesticides for a long time reported higher incidence of somatization but not psychological disorders (35). Ebrahimi et al. (2007) indicated that almost 50% of total pesticides that used in Fars province of Iran had potential of endocrine disrupting effects such as antiestrogenic, antiandrogenic, antityroidic, antigonadotropin and anti-steroid properties (63, 64). Interfering with function of endocrine system can be the base of many reproductive and developmental disorders as well as sex-related cancers. But there has been no survey exploring the link between exposure to common pesticides in Iran and prevalence of kind of diseases.

4. Conclusions

Taken together, all non-experimental studies concerning pesticide exposure in Iran fall into two categories, firstly

those dealing with detection of residues in the environment or biological samples and secondly the studies which tried to find useful biomarkers and treatments in people acutely or chronically exposed. For residue assessment in the environment, foods, and biological samples, those pesticides classified as persistent organic pollutants (POPs) like DDT derivatives and the other OCs have been mostly studied, though there are some sporadic reports on the persistence of OPs. However, most of these investigations have shown an alarming point regarding the level of widely used pesticides in the living environment, nutritional resources, and even in the samples taken from people and most seriously from pregnant or nursing women. A main concern regarding pesticides is the high prevalence of their poisoning. In comparison with other agents, pesticides have been classified as the chemicals by which poisoning is the most fatal. One reason is that pesticides are initially designed and synthesized to be toxic for biological systems. In this regard, some therapeutic approaches have been investigated for pesticides poisoning in clinic and valuable results are got.

To evaluate the effects of pesticides on human health, some valuable studies have been carried out on people chronically and occupationally exposed to these chemicals. In this respect, manifestation of the main biomarkers like decreased activity of ChE enzyme and induction of oxidative stress in accessible samples were the main findings. Oxidative stress and accompanying pathways are the main characteristics of disrupted cellular homeostasis and disease process. Moreover the relation between chronic exposure to pesticides and different types of human disease is being more uncovered (65, 66). Except one case-control study concerning higher risk of non-Hodgkin lymphoma and multiple myeloma in pesticides-exposed people, there is no other investigation on the strength of the link between exposure to pesticides and incidence of diseases in Iran. According to high extent of pesticides use during the past decade and lack of enough evidence regarding the effects of these compounds on the community, Iranian researchers need to pay more attention to diseases which are more probable to progress in the regional people in association with pesticides.

Acknowledgements

There is no acknowledgment.

Authors' Contributions

Sara Mostafalou developed the original idea, abstracted and analyzed data, and drafted the manuscript. Somayyeh Karami-Mohajeri abstracted data and drafted the manuscript. Mohammad Abdollahi conceived the study and edited the paper.

Financial Disclosure

Authors declare no conflict of interest.

Funding Support

This invited paper is the outcome of an in-house financially non-supported study. Authors thank National Elite Foundation and INSF for the support of the first author postdoc program.

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